

# Risk Factors of Hepatitis C Virus Infection in Drug Users From Eleven Methadone Maintenance Treatment Clinics in Xi'an, China

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**Background:** Hepatitis C virus (HCV) infection rates in drug users vary among different regions of China. Drug users who are unaware of their HCV serostatus tend to engage in more risky behaviors.

**Objectives:** This prospective study aimed to assess risk factors of HCV infection in drug users among 11 methadone maintenance treatment (MMT) clinics in Xi'an, China.

**Patients and Methods:** Baseline characteristics and drug use information of patients were collected upon enrollment in the study and anti-HCV tests were performed within one month after the enrollment. Data on daily medication, monthly random urine morphine test results, illicit drug use and MMT retention time were recorded during a 5-year follow-up.

**Results:** Of 10243 patients, 58.0% had positive results for anti-HCV. Injection drug use, longer duration of drug abuse, older age, female gender, unmarried status and unemployment were independent risk factors of HCV infection. Urine test positivity rate was lower (14.8% vs. 16.7%,  $\chi^2 = 100.235$ ,  $P < 0.05$ ), but MMT retention rate was higher (log-rank  $\chi^2 = 4.397$ ,  $P < 0.05$ ) in the anti-HCV positive group than anti-HCV negative one. However, multivariate regression revealed no significant association between anti-HCV serostatus and either MMT retention time or illicit drug use.

**Conclusions:** The major risk factor of HCV infection was injection drug use. The patient's awareness of his or her HCV status had a minor effect in reduction of illicit drug use and improvement in MMT retention. Therefore, adequate counseling is necessary for drug users in MMT clinics in Xi'an.

**Keywords:** Methadone; Maintenance; Treatment; Injection; Drug User

## 1. Background

The most significant risk factor of hepatitis C virus (HCV) transmission is injection drug use. Approximately 50% to 90% of injection drug users (IDUs) are seropositive for HCV (1-3). As shown in an evaluation of the first eight pilot methadone maintenance treatment (MMT) clinics (4), MMT had the potential to reduce the incidence of blood-borne infections by helping drug users to achieve opioid abstinence or decrease risky drug abuse behaviors. Interestingly, one study showed that six months of enrollment in a low-threshold MMT program reduced the proportion of injection drug use, needle sharing and drug equipment sharing among opioid users even without enforcement of abstinence-based policies (5). Individuals who continue participation or experience disrupted participation in an MMT program are less likely to inject drugs with used needles and are more likely to inject less frequently than those who left an MMT program (6). Retention of individuals in an MMT program is closely related to abstinence and decreased use of other substances (7, 8). A study by Kwiatkowski et al. (9) showed

that drug users who are unaware of their HCV serostatus tend to engage in more risky behaviors than those who are aware of their positive serological status. A young IDU's awareness of his or her HCV serostatus may have a modest effect on whether he or she engages in drug injection (10). HCV testing should be encouraged to decrease the risk among drug injectors susceptible to acquiring or transmitting HCV (11). Drug addicts' population has been increased since 1980s. Approximately 1.14 million drug addicts were registered in China in 2004 (12), and more than 75% of these were heroin users. A meta-analysis of 105 studies assessed the HCV infection rate among IDUs from 1997 to 2006 in China demonstrated that 61.4% of Chinese IDUs had positive results for HCV infection. The most severely affected areas were Hubei, Yunnan, Guangxi and Hunan provinces and the Xinjiang Uyghur Autonomous Region (13). HCV infection rate among IDUs in Yunnan is reportedly as high as 90%, and may be even higher (14, 15). Xi'an is an inland city in China and serves as a traffic hub connecting Yunnan, Sichuan, Xinjiang and other ar-

eas with high rates of drug abuse. The estimated rate of drug users sharing syringes during the most recent six months in Xi'an was about 25% lower than that observed in Chongqing, Yunnan and other regions in southwest China (16). Although HCV positivity rate is approximately 60% among drug users in Xi'an (16), the risk factors of HCV infection have not been elucidated.

## 2. Objectives

The two primary objectives of the present study were (1) to document the prevalence of HCV and the risk behaviors in drug users among 11 MMT clinics in Xi'an city and (2) to compare the rates of MMT retention and illicit drug use of patients who had positive results for HCV antibodies with those with negative results.

## 3. Patients and Methods

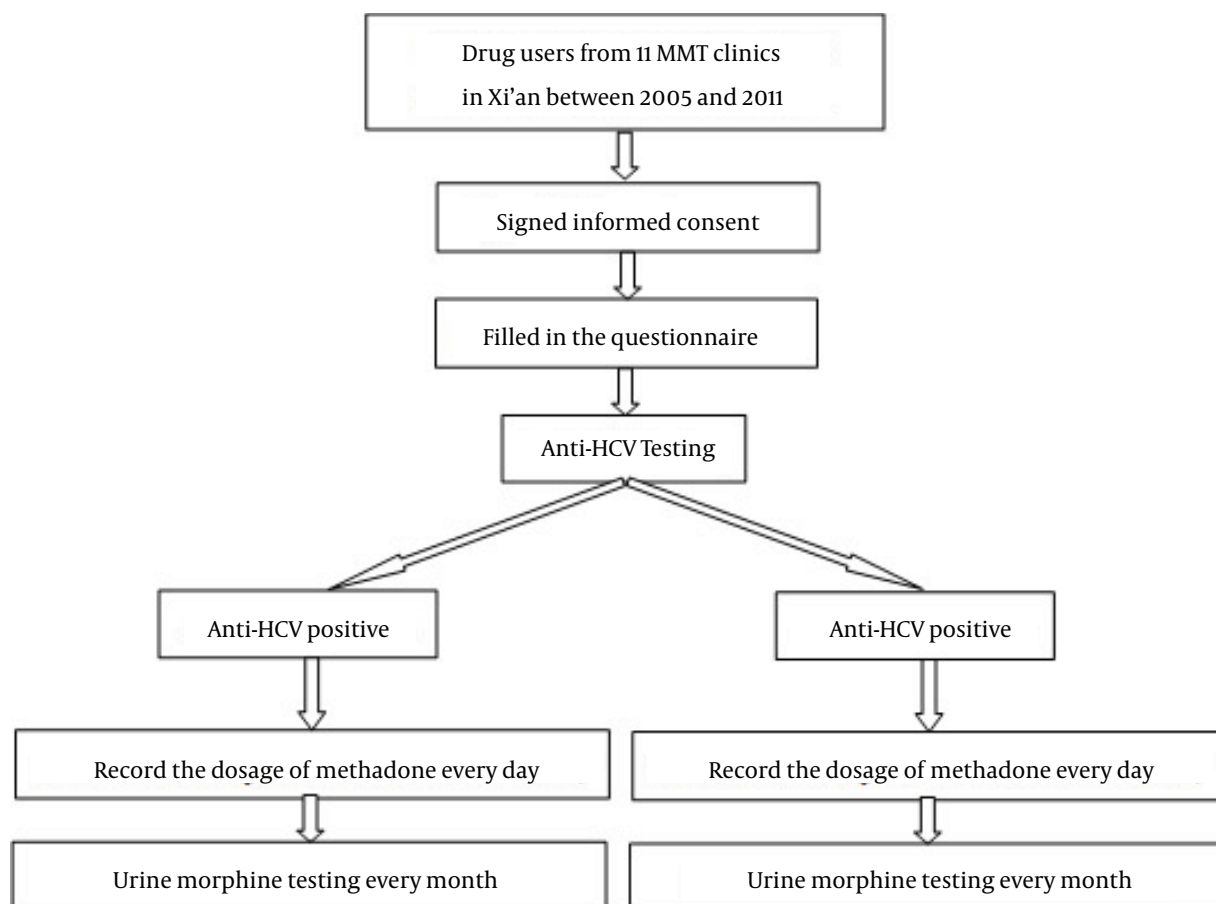
### 3.1. Patients

Eleven MMT clinics were established in Xi'an, China from October 2005 to December 2011. All drug users treated in these 11 clinics were recruited for the present study. Drug users were required to meet the following criteria

to be eligible for MMT: (1) addicted to opioids after several withdrawal treatments based on diagnostic criteria for drug dependence listed in the Chinese Classification and Diagnostic Criteria of Mental Disorders, Version 3; (2) aged > 20 years; (3) not infected with human immunodeficiency virus (HIV); (4) a local resident or a non-native local resident for more than six months; and (4) possessing full civil capacity.

### 3.2. Study Design

This study was prospectively performed. All participants were required to complete a face-to-face questionnaire with a physician in MMT clinics on the first day of study. The questionnaire assessed each patient's demographic characteristics, history of drug abuse and drug abuse behaviors. Anti-HCV tests were performed within one month of recruitment. Each day during the treatment in MMT clinics, all participants received a prescribed amount of oral methadone solution under a physician's supervision. Urine morphine tests were performed for all participants on a randomly selected day each month to check illicit drug use. Participants were followed up until 31 December 2011. The study design is shown in Figure 1.



**Figure 1.** Flow Chart of Study Design and Data Collection

### 3.3. Related Definitions

#### 3.3.1. Methadone Dosage

The average daily dosage of methadone was calculated according to the following formula:

Average daily methadone dosage = (total methadone dosage × number of days taking methadone) / total number of days taking different doses

#### 3.3.2. Illicit drug Abuse

Illicit drug abuse was determined from the most recent urine test result. A positive result from the last urine test indicated illicit drug abuse by the participant. Urine test positivity rate was calculated as the number of positive urine tests divided by total number of urine tests.

#### 3.3.3. MMT Retention Time

Dropouts were defined as patients who did not return to the MMT clinic for methadone for 30 consecutive days before 31 December 2011. Patients who remained in the MMT program included those who repeatedly exited and entered (with a discontinuation time of < 30 days) or referred from other clinics. Treatment retention was defined as number of days from admission until the patient quit treatment or until the end of follow-up.

### 3.4. Laboratory Tests

Anti-HCV antibody was detected using an HCV antibody enzyme immunoassay kit from Lizhu Diagnostics (Zhu-hai, China). HCV-seropositive participants were retested using an anti-HCV enzyme-linked immunosorbent assay kit from Beijing Wantai Biological Pharmacy Enterprise (Beijing, China) to confirm their HCV-seropositive status. Sensitivity and specificity of the kit used for confirmation from Waitai were 100.00% and 99.53%, respectively (17).

### 3.5. Statistical Analysis

Differences between groups were compared using non-parametric two-tailed Mann-Whitney U test for continuous variables and chi-squared ( $\chi^2$ ) statistic for categorical variables. Unconditional logistic regression models were used to analyze factors influencing HCV infection, methadone dosage and illicit drug use. Life tables were used to calculate cumulative retention rates and to draw retention curves. Log-rank tests were used to compare retention rates between the groups. Risk factors for MMT retention were analyzed using a Cox proportional hazard model. Statistical significance was assessed using two-sided tests with  $\alpha = 0.05$  for all analyses.

### 3.6. Ethics Statement

The study protocol was reviewed and approved by the Human Research Ethics Committee of Xi'an Jiaotong University, Xi'an, China. Before the study, the investigators explained potential risks or issues and anticipated ben-

efits to all participants and ensured that each participant understood all details of the informed consent form. Written informed consent was obtained from each participant before the study.

## 4. Results

In total, 11166 drug users underwent MMT in Xi'an from October 2005 to December 2011. Of these drug users, 91.7% (10,243) underwent anti-HCV tests. Male drug users accounted for 84.5% of these 10243 patients, and the average patients' age was 37.4 years (standard deviation, 6.7). Of all participants, 58.0% (5940) had positive results for anti-HCV test (Table 1).

### 4.1. Risk Factors of HCV Infection

The results of univariate analysis of HCV infection are shown in Table 1. HCV seropositive patients were younger, began drug use earlier and had a longer duration of drug use than HCV seronegative patients. A higher prevalence rate was observed in IDUs, patients who shared needles and those who had undergone compulsive detoxification. A relatively lower infection rate was found in patients who were male, married or had a regular partner and employed. Logistic regression analyses showed that older age, longer duration of drug use, female gender, unmarried or single status, unemployment, history of injection and history of compulsive detoxification were risk factors of HCV infection (Table 2). The major risk factor of HCV infection was injection drug use (odds ratio, 9.060 [95% confidence interval, 8.122-10.106],  $P = 0.000$ ).

### 4.2. Methadone Dosage and Correlation With HCV Serostatus

The average daily methadone dosage among all 10243 participants was 48 mg/d (ranged 6-159 mg/d). The average daily methadone dosage of HCV seropositive participants was significantly higher than that of HCV seronegative participants (50 vs. 44 mg/d, respectively;  $Z = -16.171$ ,  $P < 0.05$ ). Logistic regression analyses showed that a longer duration of drug use, female gender, ethnicity other than Han, married ones or having a regular partner, history of injection, needle sharing, compulsive detoxification and anti-HCV positivity were associated with higher methadone dosages.

### 4.3. MMT Retention Times Associated With Different HCV Serostatuses

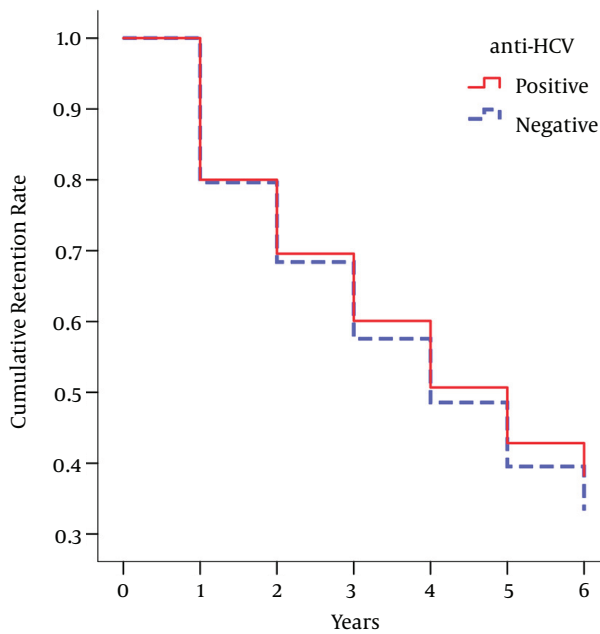
The average treatment retention time of all 10243 participants was 955 days (ranged 1-2190 days). The average retention time of HCV positive participants was significantly longer than that of HCV negative participants (986 vs. 905 days, respectively;  $Z = -5.178$ ,  $P < 0.05$ ). The 1-, 2-, 3-, 4-, 5-, and 6-year retention rates of anti-HCV positive proportional hazard model showed that older age, lon-

**Table 1.** General Information of Patients Who Underwent HCV Antibody Testing (n = 10243)<sup>a</sup>

	Total	HCV Antibody Status		Z/ $\chi^2$	P Value
		Positive (n <sub>1</sub> = 5940)	Negative (n <sub>2</sub> = 4303)		
<b>Age, y</b>	37.4 ± 6.7	37.3 ± 6.3	37.6 ± 7.1	-2.996	0.003
<b>Age at first drug use</b>	27.7 ± 7.3	26.8 ± 6.9	29.0 ± 7.5	-14.287	0.000
<b>Years of drug use, y</b>	9.2 ± 6.2	10.1 ± 5.9	8.2 ± 6.3	-16.410	0.000
<b>Gender</b>					0.000
Male	8653 (84.5)	4954 (83.4)	3699 (86.0)	12.496	
Female	1590 (15.5)	986 (16.6)	604 (14.0)		
<b>Ethnicity</b>					0.982
Han	9602 (93.7)	5568 (93.7)	4034 (93.7)	0.001	
Other	641 (6.3)	372 (6.3)	269 (6.3)		
<b>Education</b>					0.185
Elementary or lower	1053 (10.3)	590 (9.9)	463 (10.8)	3.374	
Secondary school	5346 (52.2)	3141 (52.9)	2205 (51.2)		
High school or higher	3844 (37.5)	2209 (37.2)	1635 (38.0)		
<b>Marital status</b>					0.000
Single	2910 (28.4)	1901 (32.0)	1009 (23.4)	110.462	
Married or a regular partner	5757 (56.2)	3092 (52.1)	2665 (61.9)		
Divorced, separated, or widowed	1576 (15.4)	947 (15.9)	629 (14.6)		
<b>Employed</b>					0.000
Yes	3115 (30.4)	1574 (26.5)	1541 (35.8)	102.288	
No	7128 (69.6)	4366 (73.5)	2762 (64.2)		
<b>Injection drug use</b>					0.000
Yes	7482 (73.0)	5385 (90.7)	2097 (48.7)	227.451	
No	2761 (27.0)	555 (9.3)	2206 (51.3)		
<b>Needle sharing</b>					0.000
Yes	1562 (15.2)	1161 (19.5)	401 (9.3)	201.919	
No	8681 (84.8)	4779 (80.5)	3902 (90.7)		
<b>Compulsive detoxification</b>					0.000
Yes	8910 (87.0)	5455 (91.8)	3455 (80.3)	293.666	
No	1333 (13.0)	485 (8.2)	848 (19.7)		

<sup>a</sup> Data are presented as Mean ± SD or No. (%).**Table 2.** Risk Factors of HCV Infection by Multivariate Logistic Regression Analysis

	B	SE	Wald	df	P	OR	95% CI	
							Lower	Upper
<b>Age, y</b>	0.101	0.039	6.870	1	0.009	1.106	1.026	1.193
<b>Years of drug use, y</b>	0.191	0.029	42.679	1	0.000	1.210	1.143	1.281
<b>Gender</b>	-0.250	0.065	14.876	1	0.000	0.779	0.686	0.884
<b>Marital status</b>			27.515	2	0.000			
<b>Married or regular partner</b>	-0.290	0.055	27.515	1	0.000	0.748	0.671	0.834
<b>Divorced, separated, or widowed</b>	-0.214	0.077	7.790	1	0.005	0.807	0.694	0.938
<b>Employment</b>	-0.253	0.050	25.255	1	0.000	0.777	0.704	0.857
<b>Injection drug use</b>	2.204	0.056	1562.842	1	0.000	9.060	8.122	10.106
<b>Compulsive detoxification</b>	0.453	0.071	40.302	1	0.000	1.573	1.368	1.809
<b>Constant</b>	-1.815	0.123	219.437	1	0.000	0.163		

**Figure 2.** Cumulative Retention Rates for Anti-HCV-Seropositive and -Negative Patients

Life Were Used to Draw Retention Curves. The Retention Rate of Anti-HCV-Positive Participants Was Significantly Higher Than That of Anti-HCV-Negative Participants (log-rank  $\chi^2 = 4.397$ ,  $P < 0.05$ ).

respectively, and those of anti-HCV negative participants were 0.80, 0.68, 0.58, 0.49, 0.40 and 0.33, respectively. The retention rate of anti-HCV positive participants was significantly higher than that of anti-HCV negative participants (log-rank  $\chi^2 = 4.397$ ,  $P < 0.05$ ) (Figure 2). The Cox regression analysis showed that longer duration of drug use, female gender, ethnicity other than Han, more than 9 years of education, being married or having a regular partner, unemployment, needle sharing, compulsive detoxification and higher dosages were associated with longer MMT retention times (Table 3).

#### 4.4. Illicit drug Use Compared With HCV Serostatus

In total, 160096 urine tests were performed using urine samples submitted by all 10243 participants. Of these tests, 24923 (15.6%) had positive results. The urine test positivity rate among anti-HCV positive patients was significantly lower than that among anti-HCV negative patients (14.8% vs. 16.7%, respectively;  $\chi^2 = 100.235$ ,  $P < 0.05$ ). Of 10243 participants, 9624 underwent at least one urine test. The most recent urine test result had positive result in 1949 participants, indicating an illicit drug use rate of 20.3%. Illicit drug use rate in anti-HCV positive participants was significantly lower than that in anti-HCV negative participants (19.5% vs. 21.3%, respectively;  $\chi^2 = 5.082$ ,  $P < 0.05$ ). Logistic regression analyses showed that older age, being married or having a regular partner, needle sharing and compulsive detoxification were negatively associated with illicit drug use.

**Table 3.** Multivariate Cox Proportional Hazards Model for MMT Retention

	B	SE	Wald	df	P	OR	95% CI	
							Lower	Upper
Age, y	-0.105	0.024	18.719	1	0.000	0.901	0.859	0.944
Years of drug use	-0.125	0.018	46.366	1	0.000	0.882	0.851	0.915
Gender	0.247	0.042	34.285	1	0.000	1.280	1.179	1.390
Ethnicity	-0.154	0.060	6.515	1	0.011	0.857	0.762	0.965
Education, y	-0.085	0.030	8.078	1	0.004	0.918	0.866	0.974
Marital status			9.991	2	0.007			
Married or regular partner	-0.078	0.034	5.170	1	0.023	0.925	0.865	0.989
Divorced, separated or widowed	0.035	0.048	0.546	1	0.460	1.036	0.943	1.138
Employment	0.078	0.032	6.030	1	0.014	1.081	1.016	1.150
Needle sharing	-0.292	0.042	48.892	1	0.000	0.747	0.688	0.810
Compulsive detoxification	-0.103	0.045	5.170	1	0.023	0.903	0.826	0.986
Dosage, mg/d	-0.316	0.025	157.073	1	0.000	0.729	0.694	0.766

## 5. Discussion

HCV infection rates in drug users vary among different regions because of different geographical risk factors. In the present survey, rate of injection drug use among all drug users and rate of HCV infection among IDUs were 73.0% and 72.0%, respectively; these rates were lower than the corresponding rates observed in Yunnan province (84.9% and 94.9%, respectively) (14, 15). The proportion of drug users who shared syringes in our study was also lower than that in Chongqing, Yunnan and other regions of southwestern China (16), but higher than that in Iran (18). The logistic regression data in the present study indicated that injection drug use, long-term drug use, older age, female gender, unmarried status and unemployment were independent risk factors of HCV infection. These findings were in accordance with some other studies (19-21). Moreover, certain drug-related factors, such as a history of compulsive detoxification were also independent risk factors of HCV infection. Many studies showed that transmission of HCV can occur as a consequence of sharing contaminated drug injection equipment (2, 22, 23). We found that syringe sharing was not a risk factor of HCV infection despite the fact that HCV-seropositive IDUs had an increased risk of syringe-sharing behaviors. The average daily dosage of methadone among HCV-seropositive patients was significantly higher than that of HCV-seronegative patients, suggesting that HCV-positive patients had a heavier addiction to drugs. HCV seropositivity rate in our survey (58.0%) was similar to previously reported HCV infection rate in patients undergoing MMT in Beijing (58.5%), (51.3%) Shanghai (51.3%) and Kunming (55.5%) (24, 25), but higher than patients from drop-in centers in Iran (43.4%) (18) and lower than patients undergoing MMT in Wuhan (82.3%) (26) and Hong Kong (85.0%) (27). Another study showed that fewer than a half of heroin users were still HCV-seronegative by the time they presented to MMT clinics in Xi'an, whereas drug users were likely to be infected with HCV when starting heroin within the first year and HCV positivity rate increased with the duration of drug use (28). Therefore, there remains an important opportunity to prevent new HCV infections in Xi'an. The low rate of HCV seropositivity in our survey may be explained by the fact that 91.7% (10,243) of the 11166 participants underwent anti-HCV tests and were informed about their anti-HCV test results during their first month of enrollment in the MMT program. This is in line with the finding that a young IDU's awareness of his or her HCV serostatus may have a modest effect whether he or she engages in drug injection (10). In the present study, MMT retention rate of HCV-seropositive patients was significantly higher than that of HCV-seronegative patients. In fact, the efficacy of drug abuse therapy is directly related to the duration of treatment (7), including reduction of injection drug use (8) and prevention of HIV and HCV seroconversion (29). However, multiple-factor analysis in the present study showed no correlation between MMT

retention time and HCV infection, indicating that anti-HCV serostatus had no influence on the retention time. In this study, urine test positivity rate and incidence of illicit drug abuse were significantly lower in HCV-seropositive patients than HCV-seronegative patients. This finding is in accordance with the fact that HCV-positive patients in MMT clinics are more likely to alter their injection behaviors in an effort to prevent HCV transmission (30). However, multivariate statistical analysis showed no correlation between illicit drug abuse and HCV infection, suggesting that anti-HCV serostatus had no influence on illicit drug abuse. Our findings are in accordance with some previous studies showing that patients' awareness of their HCV infection status was not associated with safer injection behaviors (31, 32). We also found that risk factors of HCV seropositivity include older age, longer duration of drug use, female gender, unmarried status, unemployment, injection drug use and a history of compulsive detoxification. Fewer than a half (42%) of heroin users were still HCV-seronegative when starting treatment in Xi'an, suggesting an opportunity to reduce the incidence of new HCV infections. Among patients involved in MMT programs, HCV-seropositive patients had higher retention rates and a lower incidence of illicit drug use than HCV-seronegative patients. However, multiple-factor analyses demonstrated no correlation between HCV infection and MMT retention or illicit drug abuse, indicating that only HCV testing had a minor effect. Therefore, high-quality counseling is necessary for this population to decrease the incidence of illicit drug use and the number of MMT clinic dropouts among IDUs susceptible to acquiring or transmitting HCV.

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## Authors' Contributions

Wang Xueliang designed the study. Wei Xiaoli managed the literature searches and supervised collection of data. Wang Lirong summarized previous related works and performed statistical analysis. Li Jinsong and Li Hengxin provided ongoing advice and technical guidance in collection of related data. Jia Wei supervised collection of data from the First Clinic of Xia'an Mental Health Center. All authors contributed and approved the final manuscript.

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